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PERSPECTIVES IN RENAL MEDICINE

Pregnancy in renal disease

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Until the 1980s, opinions conflicted concerning the reciprocal influence of kidney disease on the outcome of pregnancy and of pregnancy on the natural course of maternal renal disease. Previous studies [1–5] reported an abnormally high incidence of fetal death, but no clear picture of the factors related to fetal prognosis emerged, and whereas most authors reported a frequent deleterious effect of pregnancy on maternal renal function [3–5], others found no such adverse influence [1, 2]. However, most of the older studies were anecdotal or bore on limited series of patients, and reported on pregnancies that took place before current advances in prenatal care and antihypertensive therapy had been developed.

In the past 15 years, several studies using large numbers of patients with well defined types of kidney diseases [6–12] have considerably clarified the problem. They suggest that a clear distinction must be made between: (*i*) patients affected by primary renal diseases and those in whom renal involvement is part of a systemic disease; and (*ii*) patients having preserved renal function and normal blood pressure at conception and those with already impaired renal function and/or hypertension at the start of gestation. From these clinical studies, it was possible to identify factors that influence fetal and maternal prognosis, thus providing a basis for proper preconception counseling and optimal management of pregnancy [13]. In addition, experimental models shed light on the modifications of renal hemodynamics induced by gestation in animals with normal or altered renal function. Because impaired renal function at conception markedly increases the risk of fetal and maternal complications, problems arising in pregnant women with chronic renal failure who are on maintenance dialysis or following kidney transplantation will be specifically addressed.

PREGNANCY-INDUCED CHANGES IN RENAL HEMODYNAMICS

Experimental models

The pregnant rat is a suitable animal model for study of the gestational changes in renal hemodynamics, as recently reviewed by Baylis [14]. Pregnancy induces a state of sustained renal vasodilation, owing to the concomitant reduction in tone of both afferent and efferent arterioles, so that the increase in glomerular filtration rate (GFR) is not associated with an increase in glomerular capillary pressure (P_{GC}) [15] and no glomerular sclerosis ensues even after repetitive gestations [16]. Thus, pregnancy *per se* does not induce any deterioration in renal function in animals with a normal kidney. Moreover, gestation does not alter the course of various models of experimental renal disease such as gentamicin-induced nephropathy [17], adriamycin nephropathy [18] or of a normotensive model of glomerulonephritis [19]. Even in rats submitted to subtotal renal ablation, there was no gestation-induced worsening of renal function or accelerated glomerulosclerosis [20, 21]. However, acute blockade of nitric oxide (NO) inhibits pregnancy-induced renal vasodilation [22]. When pregnancy was superimposed on chronic blockade of nitric oxide (NO) hypertension developed, renal function declined, and endothelial damage occurred, as seen in preeclampsia [23, 24]. In summary, none of the animal models of normotensive renal disease had their gestation associated with any acute or chronic worsening of the underlying renal injury [25]. By contrast, when systemic hypertension is produced, such as by chronic NO blockade, renal and peripheral gestational vasodilation is blunted, thus suggesting a key role for NO in the hemodynamic adaptations to pregnancy [26].

Clinical data

In the healthy pregnant woman, effective renal plasma flow evaluated by PAH clearance increases by 80%, and GFR measured by inulin clearance increases by 50% from the end of the first trimester [25, 27]. These changes remain throughout pregnancy, and return to pre-pregnancy values at the end of pregnancy [28, 29]. Accordingly, serum creatinine (S_{Cr}) concentration decreases by about 10% in the first trimester and 30% in the last trimesters, with mean S_{Cr} values declining from 73 (0.82 mg/dl) pre-pregnancy to 65, 51 and 47 μmol/liter (0.73, 0.58 and 0.53 mg/dl), respectively, in the successive trimesters [27]. Therefore, a S_{Cr} value of 75 μmol/liter (0.85 mg/dl) may be indicative of incipient renal failure in pregnancy. Of note, formulae that have been proposed to estimate GFR from the S_{Cr} level, such as the Cockcroft-Gault formula [30], are not applicable during pregnancy [31]. Creatinine clearance (C_{Cr}) can be estimated using such formulae only in the preconception state or post-partum. Intravenous infusion of amino acids evokes an additional increase in GFR, indicating that renal hemodynamic reserve may be elicited in healthy pregnant women [32], but this effect was not found following an oral protein load [33].

In normal pregnancy, maternal extracellular fluid volume, especially plasma volume, continuously increases during gestation in order to provide adequate blood supply to the feto-placental unit, the increment being about 40% in plasma volume in the third

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Table 1. Fetal outcome of pregnancies in women with primary glomerulonephritis

Histology	Pregnancies/ patients	Spontaneous abortions[a]	Perinatal loss[b]	Preterm delivery[c]
Focal glomerulosclerosis	85/61	2/58 (3%)	19/81 (23%)	25/79 (32%)
Membranous nephropathy	110/70	11/95 (12%)	4/92 (4%)	28/79 (35%)
Membranoproliferative GN	165/98	23/138 (17%)	11/133 (8%)	25/134 (19%)
IgA nephritis	268/166	12/229 (5%)	36/246 (15%)	43/208 (21%)
Mesangial proliferative[d]	278/163	14/275 (5%)	32/261 (12%)	19/223 (9%)
All types	906/558	62/795 (8%)	102/813 (13%)	140/723 (19%)

Cumulative data from 6 studies [6–11]. Therapeutic abortions were excluded from calculation of pregnancy outcome. Data are from Imbasciati and Ponticelli (*Am J Nephrol* 11:353; 1991) used with permission.

[a] The series of Surian et al [7] was not considered since it does not include early spontaneous abortion.

[b] Referred to fetuses > 26 weeks

[c] Excluding the series of Abe et al [9], who do not report data on preterm deliveries and on outcomes of renal disease for each type of nephritis

[d] Including focal and diffuse proliferative nephritis [6, 9, 12].

trimester [25, 27]. Concurrently, serum albumin concentration physiologically decreases to 30 to 35 g/liter from the second trimester up to delivery. A significant relationship has been shown between the extent of plasma volume expansion and fetal growth [34], whereas preeclampsia is associated with a reduction in plasma volume [34, 35]. Parallel to gestational vasodilation, a decrease in blood pressure is observed in the first two trimesters of normal pregnancy, together with a reduced responsiveness to the pressor effects of angiotensin II [36].

PRIMARY GLOMERULAR DISEASES

Our present knowledge of fetal and maternal outcome in women with primary glomerulonephritis (GN) is mainly based on data from seven recent large studies [6–11] cumulating 906 pregnancies in 558 women diagnosed with various types of biopsy-proven primary GN. Of note, in these studies the majority of patients had normal or near-normal renal function, and the proportion of women with serum creatinine higher than 125 μmol/liter (1.4 mg/dl) at conception was less than 5%.

Fetal outcome

Overall fetal loss (not considering therapeutic abortions) was 21%, including 13% of perinatal deaths after the 26th gestational week, and the rate of pre-term delivery was 19%. Initially it was believed that the variety of glomerular disease had an influence *per se* on fetal outcome, since fetal loss and the prematurity rate differed among the various histological groups [37] as shown in Table 1. However, it subsequently appeared that risk factors associated with the renal disease account for the variable fetal outcome observed in the different types of glomerulonephritis.

Focal glomerulosclerosis and minimal change nephrotic syndrome. In focal glomerulosclerosis, an especially high fetal death rate (45%) together with a high incidence of premature delivery and intrauterine growth retardation (IUGR) was reported by the Melbourne group in patients who primarily had overt nephrotic syndrome together with hypertension at conception [38]. By contrast, European groups (including ours) reported a lower rate of fetal complications, but fewer patients had florid nephrotic syndrome, impaired renal function or hypertension early in pregnancy [7, 9, 10]. An essentially good fetal outcome was reported in minimal change nephrotic syndrome [9, 12], at least in women whose pregnancy took place when nephrotic syndrome was in remission.

IgA glomerulonephropathy. In IgAGN, the most frequent variety of primary GN, most groups report a low incidence of fetal complications, with a fetal loss rate not exceeding 7% to 13% [8–10, 39, 40]. A higher incidence of late intrauterine or perinatal deaths was reported by others, but such an adverse fetal outcome was mainly observed in patients with preexisting hypertension and/or impaired renal function [11, 41]. The presence of severe vascular lesions on kidney biopsy was highly predictive of prematurity and fetal loss [42].

Membranous glomerulonephropathy. In patients with membranous GN, three studies report a low incidence (≤ 10%) of fetal loss [8, 9, 12], but a less favorable outcome mainly due to first trimester spontaneous abortions was reported by three others [9, 43, 44] in patients having overt nephrotic syndrome and/or hypertension from the onset of gestation.

Membranoproliferative glomerulopathy. A high incidence of fetal complications was universally reported in women with membranoproliferative GN type I, with a mean fetal death rate of 25% [9, 11, 12]; most patients had preexisting nephrotic syndrome, hypertension and/or impaired renal function. In the dense intramembranous deposit (type II) variety, a favorable fetal outcome was reported in patients with preserved renal function [45, 46].

Acute post-streptococcal GN. Acute post-streptococcal GN complicating pregnancy is an unusual event. In the few cases documented by kidney biopsy [47, 48], acute GN presented as sudden occurrence of proteinuria and hematuria in late pregnancy, the diagnosis being made on high titers of antistreptolysins, antistreptokinase, and decreased C3 serum level. The outcome of gestation was successful and recovery of maternal renal function was complete.

Thus, the presently accepted concept is that fetal prognosis is not determined by the type of glomerular disease *per se*, but by the presence or absence of risk factors associated with nephropathy, namely nephrotic-range proteinuria, hypertension and/or impaired renal function present at conception or early in pregnancy [9, 13, 49].

Nephrotic-range proteinuria with marked hypoalbuminemia, when present from the first trimester of gestation, is an important factor of spontaneous abortion, prematurity and IUGR. A relationship between the degree of hypoalbuminemia and low birthweight was reported by Studd and Blaincy [50] and Barcelo et al [10]. By contrast, no significant adverse fetal outcome occurred when the nephrotic syndrome developed later in pregnancy [9,

49]. Corticosteroids, in steroid-sensitive forms of nephrotic syndrome, may improve this prognosis [48]. No developmental abnormality has been reported in neonates born to mothers who had been treated with corticosteroids or even cyclophosphamide during gestation [12, 51], but cyclophosphamide should preferably be avoided in the first trimester because it may be teratogenic when given during early pregnancy [52].

The adverse effect of hypertension on fetal outcome has long been recognized [53, 54], as the overall fetal death rate is two to three times higher in hypertensive than in normotensive pregnancies [7, 8–10]. However, this adverse effect manifests essentially when high blood pressure is present at conception or develops early in pregnancy, and therapeutic control of hypertension considerably improves fetal outcome [9, 11]. Hypertension developing late in pregnancy, even in the context of superimposed preeclampsia, usually has no deleterious impact on fetal outcome [9, 37]. Finally, impaired renal function appears to be the most deleterious factor in fetal outcome, all the more as it is most often associated with hypertension [9, 37]. Indeed, risk factors have additive effects, the most severe combination being impaired renal function together with hypertension and nephrotic-range proteinuria.

Influence of pregnancy on the course of primary GN

Increased protein excretion during pregnancy in women with preexisting GN is a common–although not constant–feature. However, such an increase is most often transient and usually reverses post-partum, because in a number of cases it only corresponds to superimposed preeclampsia [7, 9, 11]. Of note, pregnancy did not induce relapse of the nephrotic syndrome in patients with antecedent nephrosis who were in remission at conception [9, 55, 56]. Differential diagnosis is often difficult between onset of GN and preeclampsia when proteinuria associated with hypertension first manifests during pregnancy. An abnormally early onset of proteinuria and hypertension in pregnancy and their persistence beyond three months after delivery is suggestive of underlying GN [57].

Worsening of preexisting hypertension is observed in only 10 to 20% of GN patients and new-onset hypertension occurs in about 20% of pregnancies [6, 9–11]. When a pregnancy has been complicated by hypertension, there is an increased risk of recurrent hypertension in subsequent pregnancies and of development of permanent hypertension in the future, especially in patients with IgAGN [9, 41].

The most debated issue has long been whether pregnancy exerts a deleterious effect on the course of underlying GN [58]. Most early studies [1–4] and some recent ones [11, 59, 60] report irreversible deterioration of maternal renal function in pregnancy as being a frequent event, whereas most recent studies report such deterioration to be infrequent and indicate that pregnancy *per se* does not alter the natural course of maternal disease [6–9, 61].

Women with preserved or mildly decreased renal function manifest the physiological increase in GFR [6]. A transient, usually reversible, rise in S_{Cr} is often observed in late pregnancy, but an accelerated, irreversible deterioration of maternal renal function is infrequent, and is only observed in patients with already impaired renal function, severe hypertension and/or heavy proteinuria at conception, especially those with IgAGN or membranoproliferative GN [6–11].

In the long term, concordant data from recent reports suggest

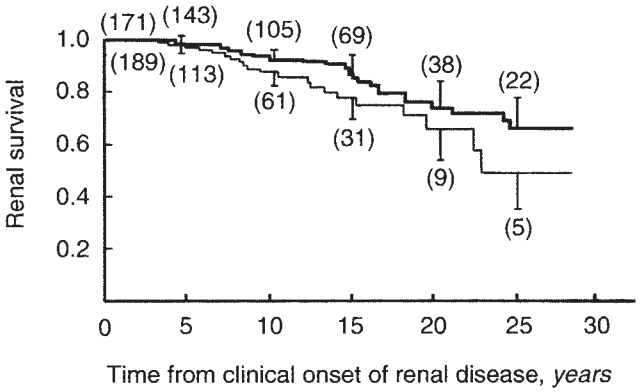

Fig. 1. Actuarial curves of renal survival free of end-stage renal failure in 360 women with primary glomerulonephritis and serum creatinine < 110 μmol/liter at conception, of whom 171 were pregnant at least once (P+; heavy line) and 189 did not conceive (P−, light line) after clinical onset of renal disease. (Reprinted with permission from Jungers et al, *Lancet* 346:1122, 1995).

that pregnancy has no deleterious effect on maternal renal disease when renal function is normal or near-normal at conception [6–9, 62]. Further evidence of this was provided by controlled studies. As reported by Barcelo et al, at the end of a five-year follow-up period the incidence of proteinuria, hypertension and renal failure was similar in 48 women with various types of primary GN who had been pregnant and in 36 who did not conceive [10]. Similarly, initial and final GFR rates did not differ between 36 women with IgAGN who had been pregnant and 35 who did not conceive over a five-year observation period as reported by Abe [63]. Decisive evidence was provided by a recent study from our group, comparing the incidence of end-stage renal failure (ESRF) among 360 women with various histological forms of primary GN who all had normal or near-normal renal function [$S_{Cr} \leq 110$ μmol/liter (1.24 mg/dl)] at conception or at presentation, who were followed for a mean duration of 15 years [64]. Actuarial renal survival curves did not differ significantly between 171 women who became pregnant after clinical onset of GN and 189 who did not conceive (Fig. 1). Furthermore, in a case-control analysis, pregnancy did not emerge as a risk factor for progression to ESRF whereas hypertension and type of GN were major determinants.

PRIMARY NON-GLOMERULAR KIDNEY DISEASES

The following reports on the various types of non-glomerular kidney diseases include mainly patients with preserved renal function, but also some patients with impaired renal function.

Reflux nephropathy

Reflux nephropathy is one of the most common renal diseases encountered in women of childbearing age. This nephropathy is frequently associated with urinary tract infection and hypertension; chronic renal failure often develops in the third and fourth decades of life [65]. Recently updated reports from the group of Kincaid-Smith [66] and our own group [67, 68] cumulate 697 pregnancies in 290 women with reflux nephropathy. The overall fetal loss rate was about 12% in both studies, which is markedly lower than that observed in women with glomerular diseases [9, 37]. Urinary tract infection (UTI) was responsible for frequent

morbidity but only resulted in deleterious consequences on fetal outcome in a very limited number of cases. The great majority of acute pyelonephritic episodes occurred in patients in whom vesicoureteral reflux was still present at the time of conception, whereas upper UTI recurred in very few women who had undergone surgical correction of vesicoureteral reflux prior to becoming pregnant [66, 68]. Therefore, it may be advisable to consider prophylactic ureterovesical reimplantation in women with persistent vesicoureteral reflux who contemplate pregnancy, at least in those who experienced repeated pyelonephritic episodes in their adult life [68].

Hypertension was of much more consequence to fetal prognosis. In our series, the relative risk of fetal loss was nearly five times higher in hypertensive than in normotensive patients, and impaired renal function at conception was the major risk factor, inasmuch as hypertension was most often concomitant [68]. A similarly adverse effect of concomitant hypertension and renal failure in women with reflux nephropathy has been reported by others [69].

Nephrolithiasis

In view of the increased urinary calcium excretion in gravidas which results in urine supersaturation for calcium oxalate and/or phosphate [70], one should anticipate that pregnancy favors calcium stone development. In fact, the concomitant increase in crystallization inhibitors, namely magnesium, citrate and nephrocalcin, that occurs during pregnancy [71] largely counterbalances gestational hypercalciuria and prevents *de novo* formation of stones during gestation.

Therefore, problems arising from urolithiasis in pregnancy essentially correspond to previously formed stones [72]. The most frequent complications are renal colic and UTI, both of which may result in premature labor. Physiological ureteropelvic dilation probably favors migration of preexisting kidney stones. Ultrasonography is the best diagnostic technique because it does not expose the fetus to ionizing radiation. Conservative management alone results in spontaneous passage of about two thirds of stones.

In the case of intractable pain, severe infection, premature contractions or deterioration of renal function, urological intervention may be needed [72]. Cystoscopy allows either removal of the stone by ureteroscopy or to relieve obstruction by placing a double J stent catheter [73, 74] that is maintained until delivery under prolonged antibacterial protection. Whenever possible lithotripsy is deferred to the post partum period, because shock waves are potentially harmful to the fetus [74].

Pregnancy in women with cystinuria may be a difficult problem. Because of the possible teratogenic effects of d-penicillamine or other sulfhydriles to the fetus, it is best to avoid using such drugs during pregnancy, especially during the first trimester [75, 76]. Prevention of cystine stone formation during pregnancy should rely on high diuresis and alkalinization by means of sodium bicarbonate [76], or best potassium citrate in hypertensive patients [72].

Autosomal dominant polycystic kidney disease (ADPKD)

The outcome of pregnancy appears essentially uneventful in ADPKD patients because the great majority of such women in the childbearing age have normal renal function. In recent studies, the mean age of female ADPKD patients was 39 years at the time of incipient renal failure [77] and 55 years at end-stage renal failure (ESRD) [78]. In three large series [9, 79, 80] the overall live birth rate in ADPKD women was nearly 85%. Hypertension when present early in gestation was the most important factor of adverse fetal prognosis and was often associated with preeclampsia and recurrence in subsequent gestations [9, 80]. Urinary tract infection was an infrequent complication and had little consequence on fetal prognosis. The number of gestations had no influence on maternal renal function in two studies [9, 79], although Gabow et al [81] reported a higher incidence of renal failure in ADPKD women who had three pregnancies or more; this effect, however, was significant only in hypertensive patients and the age of entry into ESRD was not influenced by the number of pregnancies. Screening for unruptured intracranial aneurysms by magnetic resonance angiography is advisable before conception in women having a family history of intracranial aneurysms in order to propose prophylactic repair (if indicated), and to avoid vaginal birth [82].

Other hereditary diseases

Problems of pregnancy in women with renal hereditary diseases have been recently reviewed [83].

Alport's syndrome. In the X-linked form of hereditary nephritis (Alport's syndrome) [84], carrier females usually have no or only mild urinary abnormalities during the childbearing years and pregnancy is usually uneventful, but there is a report of two sisters who developed rapidly progressive crescentic glomerulonephritis during pregnancy [85]. In the variant associated with macrothrombocytopenia and altered platelet functions gestation may be complicated by bleeding problems at delivery [84].

Tuberous sclerosis. In tuberous sclerosis retroperitoneal hemorrhage may result from bleeding angiomyolipomas during gestation [86]. In von Hippel-Lindau disease, pheochromocytomas constitute a risk of severe complications in pregnancy, especially at delivery [87]. Affected women should be screened before conceiving in order to rule out presence of pheochromocytoma, renal cell carcinoma and/or hemangioblastoma involving the central nervous system [87, 88].

In several of these severe diseases antenatal diagnosis is already available [83, 89], which gives a basis for collegiate counseling with the family and involves the nephrologist, the geneticist and the obstetrician to consider the termination of pregnancy [83].

DIABETIC NEPHROPATHY

Because insulin-dependant (type I) diabetes mellitus is a common disease, problems arising in pregnancy are of frequent concern. The presence of diabetic nephropathy impairs fetal outcome because factors related to overt microangiopathy and glycemic control add their deleterious effects to those of proteinuria and hypertension, especially in patients with already impaired renal function [90–92].

In diabetic patients with or without renal involvement, maternal hyperglycemia causes fetal hyperglycemia that results in fetal hyperinsulinemia, a factor of macrosomia and congenital malformations. In earlier reports from the Joslin Clinic [91] 40% of neonates were large for gestational age, 9% had congenital abnormalities and 8% had respiratory distress syndrome. However, careful glycemic control and advances in obstetrical and neonatal care have improved fetal survival to 90% or more in diabetic patients with normal or near-normal renal function [92], and recent case-control studies provide evidence that pregnancy

does not accelerate the onset [93, 94] or progression [95] of diabetic nephropathy.

By contrast, several groups have reported increased maternal morbidity and complicated fetal outcome in patients with overt diabetic nephropathy [91, 92, 96–98]. In all of these studies there was a high incidence of prematurity (30 to 71%), intrauterine growth retardation (16 to 22%), respiratory distress syndrome (19 to 25%) and congenital abnormalities (5 to 11%). No abnormally rapid worsening of maternal renal disease was observed in patients whose renal function was normal or near normal, even if virtually all patients experienced a marked, but reversible, increase in proteinuria and blood pressure during pregnancy [90]. In addition, successful pregnancies have been reported in diabetic patients with well-functioning kidney grafts after renal [99] or combined pancreas-kidney transplantation [100].

Fetal and maternal outcomes appear to be much more compromised in diabetic patients with overt nephropathy and impaired renal function. Studies specifically devoted to diabetic women with impaired renal function are few. A poor outcome was reported by Biesenbach, Stoger and Zazgornik in four women with diabetic nephropathy and impaired renal function, all of whom experienced an accelerated progression toward ESRD within a few years [101]. Similarly, Kimmerle et al observed an accelerated deterioration in 10 women whose renal function was already impaired, with S_{Cr} up to 215 μmol/liter (2.43 mg/dl), all of whom were hypertensive; in two women with renal transplants and $C_{Cr} \leq 35$ ml/min in early pregnancy there was accelerated transplant rejection [97]. Recently, Purdy et al reported an irreversible, accelerated progression of renal failure in 5 of 11 diabetic women whose S_{Cr} at onset of pregnancy ranged from 124 to 150 μmol/liter (1.4 to 1.7 mg/dl) [102]. Thus, pregnancy should be preferably discouraged in diabetic patients with significantly impaired renal function [97, 101, 102].

Management of pregnancy in patients with diabetic nephropathy has been recently re-evaluated [90, 102]. A multidisciplinary approach is essential, with close cooperation between the nephrologist, the diabetologist and the obstetrician. First of all, pregnancy should be planned, in order that strict control of glucose level be achieved before conception and throughout the pregnancy. Hypertension should be actively treated from the start of gestation but angiotensin-converting enzyme inhibitors (ACEIs), if previously used, should have been withdrawn [97] in order to avoid deleterious renal effects to the fetus, as discussed later. Fetal ultrasonography and echocardiography should be performed between 18 and 20 weeks of gestation to detect major developmental anomalies, giving the parents the option for termination [90].

SYSTEMIC DISEASES

Pregnancy is potentially hazardous in patients with systemic disorders because disease activity may exacerbate during gestation and because specific risk factors related to the multisystem disease add their effects to those of common factors associated with renal disease.

Lupus nephropathy

As systemic lupus erythematosus (SLE) primarily affects women of child-bearing age, the impact of SLE on pregnancy outcome is of great concern, especially when renal involvement is present.

It has long been accepted that lupus nephropathy has a major adverse influence on fetal outcome, and that pregnancy often provokes exacerbation of lupus disease. However, reports published in the past 15 years, as recently reviewed by Hayslett [103], provide a less pessimistic view. The cumulative data of several recent large studies devoted to SLE patients with renal involvement [104–109] conclude that pregnancy is most often successful and uneventful when SLE has been in stable remission for at least one year and renal function is normal at conception. In this context the overall success rate, excluding first-trimester abortions, is between 80 to 90%, but the incidence of preterm deliveries is higher than in non-SLE patients [110]. Even in patients who previously had a diffuse proliferative form of lupus nephritis, fetal outcome is most often favorable and no relapse of lupus nephritis is observed when onset of pregnancy takes place in a period of stable remission induced by therapy [104–111]. By contrast, the risk of fetal loss sharply increases when pregnancy is started in patients with active SLE, especially when the dose of prednisone needed to control disease activity is 20 mg/day or more. This is especially true when lupus nephritis first manifests during pregnancy with heavy proteinuria, overt nephrotic syndrome, hypertension and/or impaired renal function [104, 108, 109]. In such a situation, pregnancy ends in late abortion or stillbirth in about one half of the cases.

Opinions still differ widely as to the risk of lupus flare during pregnancy or post-partum. Some case-control studies comparing SLE activity in pregnant patients and in non-pregnant counterparts matched for age, duration and severity of lupus disease followed for a similar period found no difference in the incidence of lupus flares between pregnant and non-pregnant patients [112, 113], whereas another case-control study [110] and several uncontrolled studies [104–109, 111, 114] reported a higher incidence of flares during pregnancy. Such discrepancies are mainly explained by the fact that the true incidence of lupus flares in relation with pregnancy is difficult to assess, due to the largely unpredictable natural course of SLE independent of gestation [103]. However, most agree that SLE activity at conception influences the risk of relapse or exacerbation of disease activity in pregnancy. SLE exacerbations occur frequently when SLE is active at conception [104–108], whereas women in remission at conception have the lowest incidence of flares [108, 111]. Coexistence of the lupus anticoagulant or of anticardiolipin antibodies in SLE patients results in a high risk of recurrent early abortion [115], whereas the presence of anti-SSA/SSB antibodies is associated with the risk of fetal congenital heart block [114].

Preconception counseling and multidisciplinary management are essential in pregnant patients with lupus nephritis. Conception should be preferably planned in a period of stable, sustained remission for at least one year, when no corticosteroid therapy, or a low maintenance dose, is needed [103, 116]. Because anticardiolipin antibodies interfere with embryonic implantation [117], patients with such antibodies should either receive low-dose aspirin (75 to 100 mg/day) [111, 114] or low-dose subcutaneous heparin [118] from the beginning of pregnancy. Patients with severe lupus nephritis first developing or relapsing in pregnancy should be aggressively treated with high-dose corticosteroids associated with cyclophosphamide if needed [108, 109, 118, 119]. Patients with SLE in stable remission during pregnancy but with a previous history of proliferative lupus nephritis should preferably receive a course of corticosteroids in late pregnancy or at least for

two to three months post partum in order to prevent a late flare of SLE [108].

Other systemic diseases

Systemic sclerosis. In patients with systemic sclerosis, pregnancy occurring after clinical onset of the disease may result in renal crisis with abrupt hyperreninemic hypertensive oliguric renal failure and pulmonary hypertension [120], although an uneventful course of pregnancy may be observed in women with a history of systemic sclerosis in the absence of hypertension [121]. Such complications are responsible for a high rate of fetal loss and even of a fatal course in the mother [120]. However, anecdotal reports appeared of a successful fetal outcome with partial reversal of maternal renal failure when angiotensin-converting enzyme inhibitors (ACEI) were given either after delivery [122] or even during pregnancy [123]. A patient who previously had a renal crisis that reverted with ACEIs became pregnant after withdrawal of ACEIs and delivered a healthy child without a recurrence of hypertensive renal failure [124]. However, ACEIs, the only effective therapy for such renal crisis, are harmful to the fetus so that conception should preferably be discouraged in patients with overt scleroderma [83].

Polyarteritis nodosa. Since polyarteritis nodosa is uncommon in young women, no large series of pregnancies in such patients exists. The available experience, as reviewed by Owen and Hauth in 1989, was limited to 12 patients [125]. Of them, five were in remission following high-dose corticosteroids and pregnancy ended in live birth in three cases without further deterioration of maternal renal function. In the other seven cases, the disease initially manifested during pregnancy as severe preeclampsia; in all of these cases both fetus and mother died. Some advocate pregnancy termination in patients with active disease early in pregnancy [83], but aggressive treatment may be an alternative if the disease reveals later in pregnancy [125]. Successful pregnancies have been obtained in two patients with Churg and Strauss syndrome in clinical remission [126].

Wegener's granulomatosis. As Wegener's granulomatosis occurs mostly in males over 50 years of age, clinical experience in pregnancy is limited, with at best 17 cases recorded by 1996 [127, 128]. In nine patients the disease was diagnosed during pregnancy or within a few weeks of delivery; c-ANCAs were positive in most cases. Of the other eight patients in whom diagnosis was established before conception, five relapsed during pregnancy. When disease activity was controlled by corticosteroids, cyclosphosphamide and/or azathioprine, healthy babies were delivered [127, 129], in one case at the price of temporary hemodialysis [130]. Healthy twins were born to a patient after kidney transplantation while on prednisone and cyclosporine [131].

Henoch-Schönlein purpura. Little is known of pregnancy in patients with Henoch-Schönlein purpura and renal involvement. In a recent case report, a rapidly progressive glomerulonephritis associated with purpura and arthralgias developed at the end of the first gestational trimester. Renal failure worsened despite steroid therapy and oral cyclophosphamide was added from the 28th week until delivery of a premature, but otherwise normal neonate [132].

As a conclusion, in view of the frequency and harmful consequences of flares in vasculitides, pregnancy should be contemplated with extreme caution in patients with periarteritis nodosa or Wegener's granulomatosis. Whenever possible the mother should be in remission, but active disease should be treated vigorously, including by corticosteroid pulses, azathioprine and, as a last resource, cyclosphosphamide [83].

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are both characterized by microangiopathic hemolytic anemia, but may be distinguished by the following: TTP mostly develops in the second or third trimester of pregnancy with mild renal involvement and predominant extrarenal features (neurological disturbances, fever, thrombocytopenia), whereas HUS occurs usually in the immediate postpartum period, with severe acute renal failure as the prominent finding [133]. Both should be differentiated from the HELLP syndrome (acronym for Hemolysis, Elevated Liver enzymes and Low Platelet syndrome), which is associated with severe preeclampsia and involves a marked increase in serum aminotransferase level. Since more than half of cases of pregnancy-associated TTP occur before the 24th gestational week, the rate of fetal death is very high [134]. Recurrence of TTP in subsequent pregnancies has been reported [133]. Plasma exchanges alone or in combination with corticosteroid therapy have dramatically improved the prognosis in patients with the TTP/HUS syndrome [135], allowing fetal survival even in patients with onset of the syndrome in early pregnancy [136].

Familial Mediterranean fever. Patients with amyloidosis of familial Mediterranean fever may experience accelerated decline of preexisting renal failure [137]. In one patient, sarcoidosis presented in pregnancy as rapidly progressive renal failure but responded to corticosteroid therapy, with a successful fetal outcome [138].

PREGNANCY IN WOMEN WITH IMPAIRED RENAL FUNCTION

In contrast to women with normal or near-normal renal function who most often have a successful and uneventful outcome of pregnancy, gestation is much more hazardous in women with impaired renal function. Only anecdotal cases had been reported until the past decade, but five studies have now appeared that were specifically devoted to pregnancy in women with established chronic renal failure [139–143]. Adding our own series at Necker hospital which involves 43 pregnancies in 30 women [144], the available clinical experience now cumulates more than 200 pregnancies in women whose S_{Cr} level was in excess of 125 μmol/liter (1.4 mg/dl) at conception, including about one-third with $S_{Cr} >$ 200 μmol/liter (2.25 mg/dl).

Fetal prognosis

Fetal loss rate, not considering first-trimester therapeutic or spontaneous abortions, was 16% in the study of Hou, Grossman and Madias [139] on 39 pregnancies in women whose S_{Cr} ranged 124 to 221 μmol/liter (1.4 to 2.5 mg/dl), 31% in the series of Imbasciati et al [140] bearing on 19 pregnancies in women with S_{Cr} 142 to 460 μmol/liter (1.6 to 5.5 mg/dl) and 27% in the recent series of 15 pregnancies in women with GFR 42 $\pm$ 10 ml/min at conception reported by Abe [143]. In addition, in six women with reflux nephropathy, severe hypertension and S_{Cr} in the range of 200 to 310 μmol/liter (2.25 to 3.5 mg/dl) early in gestation, Becker et al observed three perinatal deaths [69].

A more favorable experience was subsequently reported by Cunningham et al [141] in a series of 37 pregnancies that took place from 1972 to 1988 in patients whose preconception S_{Cr} ranged from 124 to 832 μmol/liter (1.4 to 9.4 mg/dl). Of 26 pregnancies in patients with moderate renal failure [S_{Cr} at conception 124 to 221 μmol/liter (1.4 to 2.5 mg/dl)], 88% ended in live birth, whereas of 11 pregnancies in patients with severe renal failure [S_{Cr} at conception 230 to 832 μmol/liter (2.6 to 9.4 mg/dl)] only 7 (64%) succeeded, and there was a very high incidence of preterm delivery (86%) and fetal growth retardation (43%), the mean live-born birthweight being 1520 g [141]. Such improved fetal prognosis in the past decade was even more apparent in a recent cooperative study analyzing records from six referral centers throughout the world [142]. Among 82 pregnancies, most of which took place after 1984, in 67 women with primary renal disease whose initial S_{Cr} ranged from 124 to 487 μmol/liter (1.4 to 5.5 mg/dl), the overall live birth rate was a high as 93%. Incidence of preterm delivery was 73% and that of IUGR was 57% in pregnancies associated with the more advanced degree of renal failure [S_{Cr} > 220 μmol/liter (2.5 mg/dl) at conception] and 28 neonates required management in an intensive care neonatal unit.

In our experience the beneficial impact on fetal outcome of current advances in obstetrics and neonatology, together with coordinated obstetrical and nephrological management is evidenced [144]. Of our patients, fetal outcome was successful in 91% of pregnancies that took place after 1984 in women with primary renal diseases, which contrasts with a success rate of only 65% in the preceding 10-year period, although the proportion of women referred with advanced renal failure was higher in the recent decade. In parallel, the incidence of stillbirths decreased, whereas the proportion of successful preterm deliveries rose. The highest S_{Cr} level associated with a successful outcome, in our series was 270 μmol/liter (3.05 mg/dl), corresponding to a C_{Cr} of about 25 ml/min/1.73 m^2 (Fig. 2). Improvement of fetal outcome in the recent years was especially marked in patients with the most advanced degree of renal failure. Hypertension was the major independent risk factor related to fetal death, with a relative risk about tenfold higher in women whose MAP was > 105 mm Hg at conception than in those with spontaneous normotension or therapeutically well-controlled hypertension. Holley et al also reported hypertension as the major factor of adverse pregnancy outcome, although they did not observe an indisputable improvement in the recent years compared to previous reports, but most of their patients had diabetic nephropathy or systemic immune diseases [145].

Finally, the cumulated experience presently available allows a less pessimistic view than was held not long ago. Successful fetal outcome may now generally be expected whenever the S_{Cr} at conception is under 160 to 180 μmol/liter (1.81 to 2.03 mg/dl; corresponding to a creatinine clearance of about 40 ml/min/1.73 m^2), and is also frequent in patients with S_{Cr} up to 200 to 250 μmol/liter (2.2 to 2.8 mg/dl; corresponding to a C_{Cr} of 25 to 30 ml/min/1.73 m^2), although fetal and maternal outcomes still remain much more hazardous beyond this limit. However, in recent years, several reports appeared of patients with advanced renal failure at conception in whom hemodialysis or peritoneal dialysis had to be started during pregnancy in order to limit uremic toxicity, and who successfully delivered live infants, usually very premature and of very low birthweight [146–150]. It must be stressed that, in most cases, supportive therapy had to be pursued after delivery because deterioration of maternal renal failure was irreversible [147, 150]. Earlier initiation of supplementing dialysis, that is, as soon as S_{Cr} exceeds 350 μmol/liter (4 mg/dl), has been reported to allow better fetal growth and prevent prematurity [151].

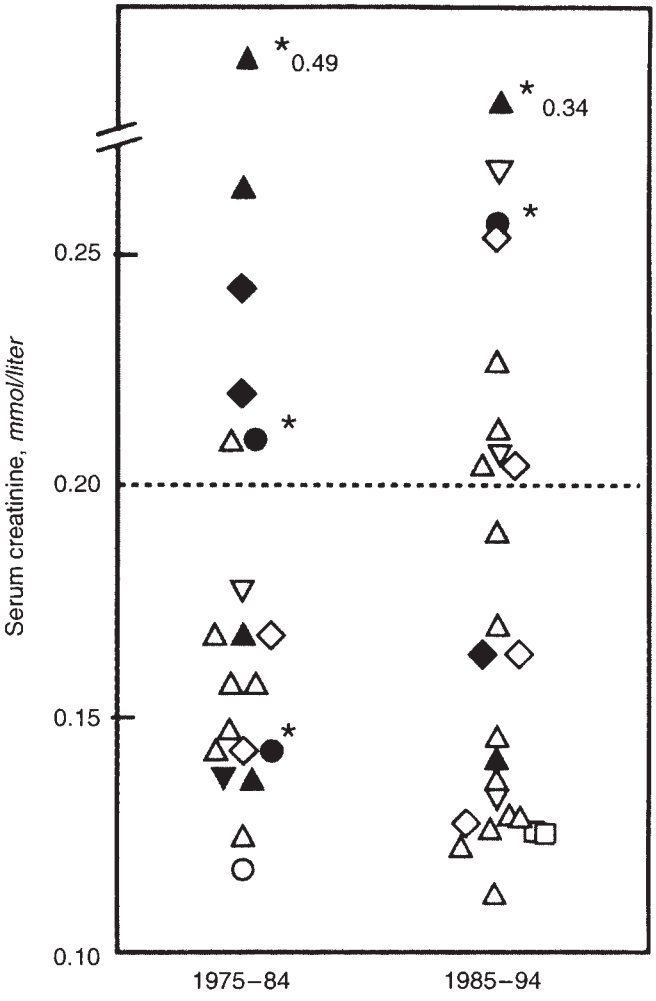

Fig. 2. Outcome of 43 pregnancies in 30 women with impaired renal function followed at Necker hospital. Fetal outcome is compared in the 1975 to 1984 and 1985 to 1994 decades with respect to serum creatinine level at conception and primary renal disease. Open symbols denote live births, closed symbols denote fetal death with asterisks indicating first-trimester abortions. Renal disease is represented as follows: (◇) polycystic kidney disease; (△) reflux nephropathy; (▽) chronic interstitial nephritis; (○) IgAGN; (□) membranous GN. (Used with permission from Jungers et al [144].)

Maternal outcome

Gestational increase in GFR, although of a lesser extent than that seen in normal gravidas, may be observed in women with moderately impaired renal function but in none with severe renal dysfunction [141, 144]. Superimposed preeclampsia is a frequent complication in women with impaired renal function, especially those with preexisting permanent hypertension. In this setting, superimposed preeclampsia developed in 65% of pregnancies in our patients [144], and in 57 to 80% in other series [139–141].

The most crucial issue is whether or not there is an increased

risk of irreversible worsening of maternal renal disease in patients with already impaired renal function. Such an accelerated course was observed in nearly half of patients whose S_{Cr} ranged from 142 to 257 μmol/liter (1.6 to 2.9 mg/dl) reported by Hou et al [139] and in the same proportion in patients with preconception S_{Cr} level ranging from 159 to 407 μmol/liter (1.8 to 4.6 mg/dl) reported by Imbasciati et al [140] and in patients with preconception GFR lower than 50 ml/min reported by Abe [143], as well as in all of six patients with S_{Cr} ranging from 200 to 310 μmol/liter (2.25 to 3.5 mg/dl) reported by Becker et al [69]. In the study of Cunningham et al, such accelerated deterioration was observed in only 5 (19%) of 26 patients with $S_{Cr} < 230$ μmol/liter (2.6 mg/dl), contrasting with 5 (45%) of 11 patients with S_{Cr} ranging from 230 to 832 μmol/liter (2.6 to 9.4 mg/dl) [141].

In our series [144], accelerated worsening of maternal disease was observed in 7 of 30 women (23%), all of whom had severe hypertension and heavy proteinuria at conception; all but two had an initial S_{Cr} in excess of 210 μmol/liter (2.37 mg/dl). As compared to the preconception level, late in pregnancy a rise in S_{Cr} was observed, of 21% as a mean, which usually reverted within two to four months of delivery to a value slightly higher than the preconception level. The lack of such a post partum reversal in the S_{Cr} level was predictive of relentless accelerated progression toward ESRF. In the cooperative study of Jones and Hayslett, the S_{Cr} level increased from a mean value of 168 ± 71 μmol/liter (1.9 ± 0.8 mg/dl) early in pregnancy to 221 ± 115 μmol/liter (2.5 ± 1.3 mg/dl) in the third trimester, a rise of 31%. An accelerated course toward ESRF was observed in 7 (35%) of 20 pregnancies in women whose initial S_{Cr} concentration was 177 μmol/liter (2 mg/dl) or higher [142].

There is no clear-cut limit of renal dysfunction beyond which the risk of accelerated deterioration sharply increases, but present evidence suggests that the risk begins when S_{Cr} is in excess of 180 μmol/liter (2 mg/dl), and that a S_{Cr} value in excess of 250 μmol/liter (2.8 mg/dl), or C_{Cr} below 25 ml/min/1.73 m^2, is indicative of a high potential of deterioration, particularly when severe hypertension and/or heavy proteinuria is present, especially in patients with primary glomerulonephritis or systemic disease. Guidelines to optimal management of pregnancy in women with impaired renal function are summarized in Table 2.

Table 2. Guidelines to optimize pregnancy outcome in women with impaired renal function

1. Full preconception counseling and planned pregnancy.
2. Closely coordinated care between nephrologist and obstetrician.
3. Management of pregnancy in a high-risk obstetric facility with attendent neonatal intensive care unit.
4. Optimal blood pressure control from the beginning of pregnancy: avoidance of diuretics and ACEIs; preferred use of methyldopa and beta-receptor antagonists as first- and second-line drugs; diastolic blood pressure no higher than 90 mm Hg and no lower than 80 mm Hg.
5. Correction of anemia: iron and folate supplementation; institution or reinforcement of EPO therapy.
6. Prevention of metabolic acidosis and hypocalcemia.
7. Adequate protein and calorie supply.
8. Intensified surveillance of serum creatinine and urea level. Initiation of supplemental dialysis whenever S_{Cr} is in excess of 350–400 μmol/liter and/or blood urea in excess of 20 mmol/liter.
9. Intensified fetal monitoring from the 26th gestational week; hospitalization of the patient in a high-risk obstetrical facility in the case of premature contractions.
10. Close surveillance of maternal renal function, blood pressure and proteinuria in the post-partum period.

PREGNANCY IN WOMEN ON MAINTENANCE DIALYSIS

Pregnancy was reported as very infrequent, and both unsuccessful and complicated, in women on maintenance dialysis. However, in the recent years, a prudently more optimistic view has been progressively emerging, in parallel with improvement in the general condition of patients on maintenance dialysis and better management of the dialysis patient who desires motherhood, as recently reviewed by Hou [152].

Fertility in ESRD patients

Fertility is decreased in ESRD patients, due to uremia-associated hypothalamo-pituitary dysfunction resulting in ovarian dysfunction and anovulatory cycles [153, 154]. However, improved dialysis efficacy together with correction of anemia due to the generalized use of recombinant erythropoietin presently allows better restoration of general condition and sexual function, and results in an increased frequency of ovulatory cycles and augmented fertility [155]. As a consequence, appropriate contraception is now needed in female dialysis patients of childbearing age in order to avoid an unplanned or unwanted pregnancy, which often carries the risk of an unsuccessful outcome, and creates severe emotional stress in the patient [152]. The diagnosis of pregnancy can be difficult and is frequently made late. In some instances, pregnancy was diagnosed upon increasing anemia or apparent resistence to recombinant erythropoietin therapy [156]. Urine pregnancy tests are of no value, even when residual urine output is still present. Measurement of serum β human chorionic gonadotrophin level is also inaccurate, so that ultrasonography is the only valuable means to assess gestational age [152].

Fetal outcome

By the end of 1993, there were about 75 isolated reports of successful pregnancies in women on hemodialysis or peritoneal dialysis, as reviewed by Hou [152], but few studies allow an accurate evaluation of the frequency of gestation and its outcome in the whole population of dialysis women. In 1980, 115 pregnancies were reported among 13,000 women of childbearing age followed in Europe; 45 ended in termination of pregnancy and of the other 70 only 16 (23%) resulted in live birth [157]. In 1992, Souqiyyeh et al reported a live birth rate of 30% among 27 pregnancies that occurred in 22 dialysis patients over the previous five years [158]. More recently, Hou completed an inquiry in 194 dialysis units in the USA caring for 1281 women of childbearing age [159]. Sixty pregnancies were reported, of which 37% resulted in surviving infants. Interestingly, the success rate rose from 21% prior to 1990 to 52% in 1990 to 1991, thus reflecting considerable progress in the management of pregnant dialysis patients (Fig. 3).

Prematurity is the major problem in dialysis pregnancies, with a continuum between mid-trimester intrauterine fetal deaths, stillbirths, and premature live births [159]. Most living neonates are of

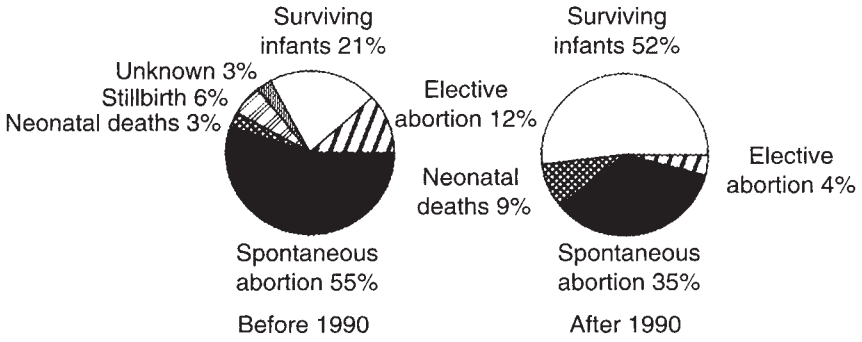

Fig. 3. Outcome of pregnancy in women on maintenance dialysis. Thirty-six pregnancies (left panel) occurred before 1990, and 24 (right panel) in 1990 to 1991. (Used with permission from Hou S, *Am J Kid Dis* 23:60, 1994.)

very low birthweight, indicating the need for management of gestation in high-risk pregnancy facilities with attendent neonatal intensive care unit. A beneficial effect of indomethacin given in the case of premature uterine contractions has been reported [150], but its prolonged use has been complicated by neonatal anuria and stillbirth [160], and this drug should never be prescribed beyond the 32th gestational week. Many nephrologists currently discourage its use since it carries the risks of neonatal renal failure, necrotizing enterocolitis, intracranial hemorrhage and premature ductus arteriosus closure [161].

Polyhydramnios is common in dialysis patients, probably as a result of the osmotic diuresis induced by the high blood urea concentration delivered to fetal kidneys where renal function is normal [150]. Daily dialysis with blood urea maintained under 17 mmol/liter and slow ultrafiltration has been proposed to prevent polyhydramnios and reduce the fetal azotemic environment. In addition, prophylactic dialysis allows easier control of hypertension and more liberal protein intake by the mother [152]. Anemia of renal failure worsens during pregnancy, because the decline in hematocrit due to plasma volume expansion adds its effects to the lack of increased red cell production. A generally accepted goal is to restore maternal blood hemoglobin level to 10 to 11 g/dl by institution or reinforcement of recombinant erythropoietin therapy [152]. Of note, recombinant erythropoietin requirement usually increases by about 50% in pregnancy [148, 149, 156].

Management of dialysis in pregnancy

Managing pregnancy in dialyzed patients is a difficult task, requiring especially close cooperation between nephrologic and obstetric teams. Measures aimed at optimizing fetal and maternal outcome, as discussed in detail by Hou [152], are summarized in Table 3. Whether hemodialysis or peritoneal dialysis is the most appropriate in pregnant patients is debated. Both techniques, when carefully managed, appear of value and neither is clearly better than the other. Doppler velocimetry of the uterine and umbilical arteries at 20 to 24 weeks of gestation are of interest to predict the risk of preeclampsia and evaluate the effect of hemodialysis on the utero-placental and umbilical-placental circulations [162, 163].

PREGNANCY IN RENAL TRANSPLANT RECIPIENTS

By contrast with patients on dialysis, in whom pregnancy still is an infrequent event, thousands of successful gestations have occurred in transplant recipients throughout the past four decades [164]. A number of transplanted women even had more than one successful pregnancy [165]. Indeed, transplantation rapidly reverses the impaired fertility associated with ESRD and restores libido and sexual activity. Thus, transplant recipients of childbearing age should be informed that they are able to conceive and should receive appropriate contraception.

Table 3. Guidelines to optimize pregnancy outcome in the pregnant dialysis patient

1. Prophylactic dialysis: blood urea maintained below 17 mmol/liter to avoid polyhydramnios.
2. If hemodialysis is used: 5 to 7 dialysis sessions per week, with bicarbonate buffer, minimal heparinization and slow-rate ultrafiltration, in order to avoid dialysis hypotension and volume contraction.
3. If peritoneal dialysis is used: decrease exchange volumes (e.g., to 1.5 liter) and increase exchange frequency.
4. Adequate calorie and protein supply: protein intake of 1 g/kg/day plus an additional 20 g/day for fetal growth requirement; supplements of hydrosoluble vitamins and zinc.
5. Adaptation of antihypertensive treatment (cf. Table 2).
6. Correction of anemia: supplements of iron and folic acid; hemoglobin level no lower than 10 to 11 g/dl, with institution or reinforcement of EPO therapy (requirements are 1.5 to 2 times higher in pregnancy) whenever needed.
7. Prevention of metabolic acidosis.
8. Prevention of hypocalcemia by oral calcium carbonate supplementation; avoidance of end-hemodialysis hypercalcemia.
9. Treatment of premature labor: prefer beta-agonists as first-line drugs; NSAIDs to be used with great caution and for a limited duration.
10. Reinforced fetal monitoring as soon as viability is reached.

Fetal perspective

Overall, of 3382 gestations in 2409 renal allograft recipients recorded in a survey of the world literature from 1961 to 1994 [164], 34% terminated in therapeutic (20%) or spontaneous (14%) abortion, but 93% of the gestations that continued beyond the 20th gestational week ended successfully. However, the incidence of preterm delivery (50%) and of growth retardation (40%) with neonates of very low birth weight was high. Factors influencing fetal outcome are essentially the same as in women with parenchymal renal disease. Hypertension, particularly when

Table 4. Preconception guidelines for renal allograft recipients

1. Good general health for two years post-transplant.
2. Stable renal function with plasma creatinine <2 mg/dl (≈ 180 μmol/liter) and, preferably, <1.5 mg/dl (≈135 μmol/liter).
3. No evidence of graft rejection.
4. No or minimal proteinuria.
5. Absent of pelvicaliceal distension on a recent urogram or echography.
6. Absent or easily managed hypertension.
7. Drug therapy reduced to maintenance levels: prednisone ≤ 15 mg/day, azathioprine ≤ 2 mg/kg/day, cyclosporine A ≤ 5 mg/kg/day.

present at conception, is associated with an adverse perinatal outcome [166]. Successful fetal outcome was achieved in 96% of pregnancies started with a S_{Cr} < 125 μmol/liter (1.41 mg/dl), whereas this proportion fell to 75% in patients whose preconception S_{Cr} level was in excess of this value, the upper S_{Cr} level associated with a successful outcome being 160 to 180 μmol/liter (1.8 to 2 mg/dl) [164].

No abnormally high incidence of developmental abnormalities has been reported in babies born to patients receiving either azathioprine at a daily dose ≤ 2 mg/kg/day, or cyclosporine A up to 5 mg/kg/day [167]. A longer interval between successful transplantation and conception is associated with a lower incidence of prematurity and low birthweight [168, 169], and an interval of at least two years is a generally accepted recommendation [164]. Table 4 summarizes preconception guidelines for renal allograft recipients as recommended by Davison [164].

Effect of pregnancy on allograft survival

Increases in GFR and renal plasma flow characteristic of normal pregnancy are seen in transplant recipients, although to a lesser degree [170]. The crucial question, however, is whether pregnancy induces a risk of deterioration of graft function. Several studies evaluated this risk by comparing long-term graft function in pregnant and matched non-pregnant women. Salmela et al reported a higher increase in S_{Cr} after pregnancy and a poorer ten-year graft survival in 22 transplant patients who became pregnant than in matched transplant women without pregnancy [171]. However, other groups did not find a deleterious effect of pregnancy on graft function. Rizzoni et al compared 53 pregnant and 53 non-pregnant female transplant recipients over a four-year follow-up period and disclosed no increased rate of graft deterioration in pregnant women, provided S_{Cr} was < 160 μmol/liter (1.8 mg/dl) at conception [172]. Sturgiss and Davison compared 18 pregnant versus 18 non-pregnant women over a mean observation period of 12 years [173], recently up-dated to 15 years [174], and found that the mean S_{Cr} values over the entire follow-up did not significantly differ between the two groups. First et al compared 18 women who became pregnant with 26 non-pregnant women and 23 male transplant recipients; graft survival with a mean post-transplant follow-up of 12 years did not differ among the three groups [175]. Such concordant results authorize the conclusion that pregnancy does not have a deleterious long-term effect on graft survival, at least when the grafted kidney is functioning well.

MANAGEMENT OF PREGNANCY IN WOMEN WITH KIDNEY DISEASE

The main lesson gained from recent studies is that every pregnancy in a woman with renal disease, especially when impaired renal function and/or hypertension is present, is a high-risk pregnancy. Optimal management implies a multidisciplinary approach, the patient being followed in a tertiary care obstetrical facility with experience in the care of high-risk pregnancies and with an attendant neonatal intensive care unit, under the closely coordinated care of the nephrologist and the obstetrician from conception throughout the whole pregnancy [13, 176].

Preconception counseling

Whenever possible, pregnancy should be planned in order that conception takes place at a time when predictable risks are minimal. Patients with primary renal disease and normal or near normal renal function [S_{Cr} < 110 μmol/liter (1.24 mg/dl)] have few contraindications to pregnancy [6, 9, 13]. Patients with systemic disease such as SLE or vasculitis should preferably conceive after a stable remission has been obtained for at least one year [103, 108, 116]. Patients with diabetic nephropathy should achieve optimal glycemic control prior to conceiving [90, 96].

The most difficult decision concerns patients with already impaired renal function. Pregnancy should be preferably undertaken before S_{Cr} has reached 180 to 200 μmol/liter (2.03 to 2.26 mg/dl), or C_{Cr} 40 ml/min/1.73 m^2, in patients with primary glomerular or non-glomerular renal diseases. Successful outcomes have been obtained with S_{Cr} in excess of this level [141–144], but both the risk of prematurity and fetal growth retardation, and of accelerated deterioration of maternal renal function are high when S_{Cr} exceeds 250 to 300 μmol/liter (2.8 to 3.4 mg/dl). In patients with diabetic nephrophathy, a S_{Cr} level compatible with an acceptable risk for the fetus and maternal renal function is probably lower and pregnancy should preferably be discouraged when S_{Cr} is above 130 to 150 μmol/liter (1.5 to 1.7 mg/dl), especially if severe hypertension coexists [101, 102]. In patients with advanced renal failure or already on maintenance hemodialysis or peritoneal dialysis, although a successful fetal outcome is now less exceptional than in the recent past, it is often advisable to defer pregnancy to after a successful transplantation [13, 83].

Patient and spouse must be clearly and comprehensively informed of all the perspectives of pregnancy with respect to expected fetal outcome and course of the maternal renal disease. The final decision should be taken by the patient and spouse after receiving full information [13].

Diagnosis of renal disease in pregnancy

By definition, preconception counseling is not feasible in patients in whom renal disease first manifests during pregnancy. Presenting manifestations are proteinuria, the nephrotic syndrome, hypertension and/or elevated S_{Cr}. Such a constellation of signs often mimics preeclampsia, especially when occurring in the latter half of pregnancy. Antepartum kidney biopsy has been advocated by some authors [177], but most nephrologists restrict biopsy to cases of rapidly progressive deterioration of renal

function or of intense nephrotic syndrome occurring prior to 32 weeks of gestation [178]. The transjugular route may be preferred in patients with thrombocytopenia and/or coagulation disorders.

Management guidelines

The most important factor of fetal prognosis, besides the level of maternal renal function, is blood pressure. Most nephrologists now agree that high blood pressure, especially when preexisting or developing early in pregnancy, should be treated more aggressively in patients with underlying renal parenchymal disease than in patients with isolated essential hypertension [10, 13, 83]. The problem of the optimal blood pressure level to achieve in pregnant patients with underlying renal disease, however, is still debated. In our experience, the best fetal outcome in hypertensive patients was observed when diastolic blood pressure could be maintained therapeutically between 80 and 90 mm Hg.

The choice of the antihypertensive agent is important. This topic has been recently reviewed [179–181]. There is consensus that alpha-methyldopa should be used as the first-line agent because its safety is well documented. Second-line agents added to methyldopa may include the combined β and α-adrenergic blocker labetalol, or beta-blockers such as pindolol, metoprolol or oxprenolol. Atenolol has been reported to adversely affect fetal growth [181]. Although long-term studies on the tolerance of hydralazine and calcium-channel blockers are not available, these drugs may be used in patients insufficiently reponsive to the above-mentioned, better studied drugs. Diuretics should be best avoided in pregnancy in order to prevent volume contraction. ACEIs, which may induce irreversible anuria in the neonate and are possibly teratogenic are contraindicated in pregnancy, at least in the last two trimesters [182, 183]. Calcium supplementation has been reported to improve blood pressure and prevent preeclampsia [184], and is especially indicated in dialysis patients [146, 152].

Use of low-dose aspirin to prevent onset of preeclampsia is debated. Because the relative risk of preeclampsia is at least five times greater in patients with preexisting hypertension, low dose aspirin (75 to 100 mg/day) should be indicated in hypertensive patients from the 12th week of pregnancy [179], and earlier in SLE patients with the presence of anticardiolipin antibodies or the lupus anticoagulant, even in the absence of hypertension, to prevent placental infarction and ischemia [111, 114].

Fetal monitoring and delivery

Serial assessment of fetal growth and well-being is essential in pregnant patients with renal disease because of the increased risk of intrauterine growth retardation and stillbirth [13, 83]. Uterine artery waveform indices at 19 to 24 weeks gestation may be useful for the prediction of preeclampsia and IUGR [185], although definitive evidence is still lacking. Fetal growth should be ultrasonographically screened beyond 26 weeks of gestation. If IUGR is detected, fetal well-being evaluations including fetal cardiotocography, amniotic fluid index, umbilical artery and fetal cerebral arteries velocity should be performed [176].

A substantial proportion of neonates born to mothers with impaired renal function are very premature, and often of very low birthweight. Extreme prematurity is associated with a high perinatal mortality rate, and few infants born before the 25th gestational week survive without severe encephalic sequelae [186]. Morbidity and mortality of immature neonates are related to peri- or intraventricular hemorrhage, periventricular leukomalacia, retinopathy, enterocolitis, chronic lung disease and acute respiratory distress syndrome. Only the latter is preventable by antenatal glucocorticoid administration, which is indicated when gestational age is critical (25 to 34 weeks) in order to enhance fetal pulmonary maturation [187]. Betamethasone or dexamethasone should be given every 12 hours for two days. The resulting reduction in respiratory morbidity is associated with reductions in neurological complications.

In cases of threatening premature contractions, beta-adrenergic receptor agonists may stop premature labor for a few days and thus allow antenatal corticosteroid administration. If the use of beta-adrenergic agonists is contraindicated, especially in hypertensive patients, nifedipine should be used [188]. As discussed above, non-steroidal antiinflammatory drugs should be used with great caution. Although indomethacin has been considered a useful tool to treat premature labor, many neonatologists currently discourage its use since it carries the risk of neonatal renal failure, in addition to premature closure of the ductus arteriosus. Corticosteroids may be given during lactation. However, breastfeeding is contraindicated in women receiving non-steroidal antiinflammatory drugs, cyclosphosphamide, azathioprine, cyclosporine or antimalarial drugs [189–191].

CONCLUSION

In conclusion, the present state of our knowledge supports a more optimistic view of pregnancy in patients with renal disease than in the recent past, especially with respect to fetal outcome [192]. Factors governing fetal and maternal prognosis are now well defined. In the majority of patients with primary renal disease who have preserved renal function and well-controlled blood pressure, pregnancy is essentially successful and does not alter the natural course of maternal renal disease. Even in patients with already impaired renal function and/or hypertension, fetal outcome has significantly improved in recent years thanks to continuous progress in obstetrics and neonatology and better management of hypertension and renal failure. A risk of unsuccessful fetal issue and of deterioration of maternal renal disease still persists, however, of which the patient and spouse must be clearly informed. Multidisciplinary management, preferably in a tertiary care facility, with close coordination between the nephrologist and the obstetrician from the beginning of gestation is the key factor to optimize the issue of such high risk pregnancies. In view of the continuing progress in obstetrics and neonatology, as well as in our knowledge of factors governing fetal development in a hostile hypertensive and/or uremic milieu, one may expect that an increasing number of women in the near future will be able to obtain motherhood despite underlying renal disease.

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